

A High Resolution FISH Map of Human Chromosome 19 Provides a Metric Backbone For Integration of Physical and Genetic Markers and Assembly of Sequence-Ready Clone Maps

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More than 40 previously unmapped cosmids, many probe-positive for genes and informative genetic markers, have been strategically added to a high resolution fluorescence *in situ* hybridization (FISH) metric map of human chromosome 19 (Brandriff, et al., *Genomics* 23:582-59, 1994; Gordon et al., *Genomics*, in press, 1995); linear order of and distance estimates between neighboring cosmids have been established for 236 cosmids and order is known for over 60 additional cosmids. The current estimate of the combined length of unique sequence portion of both arms of chromosome 19 represented by the map is about 51 Mb with the average interval size between reference cosmids approaching 210 kbp. This map provides a metric backbone that facilitates assembly of BACs, PACs, P1s and cosmids into sequence-ready islands of continuous bacterial-based clones.

The location of new cosmids was determined using standard FISH techniques applied to a series of chromatin targets with increasing resolution. In addition, application of a new technique involving borate swollen interphase nuclei (Yokota et al., *Genomics* 25:485-491, 1995) provided an extended chromatin substrate for three cosmid ordering in two or three colors. The highly extended chromatin in human sperm pronuclei provided confirmation and refinement of order between closely spaced probes and the establishment of distance estimates between cosmids.

The order of and distance between ~150 polymorphic markers (~100 markers with heterozygosities of >0.50) have been determined through inclusion of probe positive cosmids in the FISH metric map. The incorporation of these markers into the physical map resolves the order of tightly linked genetic markers, provides estimates of physical distance between markers and integrates the different linkage maps. The integration of genetic markers into the high resolution FISH metric map and the localization of over 110 genes, combined with approximately 42 Mb of associated EcoRI restriction maps for which order and distance between islands is known, provides sequence-ready clones that are a unique resource for isolation and sequencing of mapped disease genes.

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